Exhibit D

A human pluripotent neuroepithelial cell line was developed by means of culturing primary human fetal cortex of 12 weeks gestation obtained from elective termination under a London Teaching Hospital Ethical Committee approved protocol and following guidelines set out in the Polkinghorne Report (Review of the Guidance on the Research Use of Foetuses and Foetal Material presented to Parliament July 1989, London, HMSO). The primary cells were plated on laminin-coated flasks and infected after attachment with an amphotropic virus encoding the temperature-sensitive SV40 tsA58-U19 mutation gene. Following 4 weeks of expansion at the gene-permissive temperature (33° C), several colonies of Tag-positive cells emerged. Following cell purification, clones were ringed, picked and expanded. One of these lines, RCB5600OGCX (herein abbreviated to CX), was found to be positive for a range of neuroepithelial stem cell markers, including nestin and musashil. This line was conditional to temperature, showing growth at 33° C, but no growth and partial differentiation at 37° C. It was confirmed as clonal by Southern blotting, with a single integration site for the tsTAg gene.

Effects of the human conditionally immortal clonal cell line (CX) were assessed in rats with unilateral basal forebrain excitotoxic lesions of the cholinergic projections from basal forebrain to cortex. This lesion mimics some of the cell loss that occurs in Alzheimer's disease and other neurodegenerative conditions, and gives rise to robust deficits in learning and memory tasks, including spatial learning in the water maze. The water maze task requires rats to find a submerged platform located in the center of one quadrant in a large (200 cm diameter) circular swimming pool.

In the first study (AD5), effects of the human line were assessed in comparison with several murine cell lines, including MHP36 reported here as a positive control, and with sham-grafted lesioned and non-lesioned controls. Rats received unilateral injections of AMPA (0.3 μl in two sites: rostral and caudal) into the basal forebrain nucleus basalis magnocellularis (nbm). Non-lesioned controls received vehicle at the same sites. Twenty-one days after lesioning, rats received unilateral cell suspension or sham vehicle grafts (n per group = 10) into the frontal and parietal cortex, the terminal regions of cholinergic basal forebrain projections. These sites have been associated with substantial

graft-induced behavioral recovery in this lesion model. Eight weeks later, all groups were trained to find a submerged platform in a water maze test where poor performance across several parameters (latency to reach the platform, distance swum and time spent in appropriate sectors) reflects spatial long- and short-term learning and memory impairments. The lesion-only group showed little improvement over 14 days, taking 45 seconds to reach the platform by the end of training, compared with c. 15 seconds by controls. Rats grafted with the murine MHP36 cell line performed significantly better than lesioned animals. However, rats receiving the human cell line (CX) showed as rapid spatial learning as controls, and were superior both to the lesion and the murine grafted groups. On the probe trial, with the platform removed, which tests memory for its location by time spent searching in the appropriate sector, controls and rats grafted with human and murine cell lines spent 40%-50% of time in the platform quadrant, showing comparable good recall of its position, whereas lesion-only rats spent 25% of time there, showing chance level recall. The superiority of human and murine grafted groups relative to lesion-only animals was seen also in a working memory task of rapid spatial learning, when the position of the platform was changed each day.

In order to replicate the substantial positive effects of the human cell line 500 CX, a second study (AD6) was carried out comparing grafted rats with sham-grafted lesioned and non-lesioned controls. Lesion, grafting and testing parameters were the same as those in the previous experiment (AD5) with the exception that rats were tested at six rather than eight weeks after grafting. Results of the two experiments were highly comparable. Spatial learning in grafted rats was as efficient as in controls in all parameters; probe trial performance showed good recall of the platform position in control and grafted groups and poor memory in lesioned rats, whilst working memory in control and grafted groups was also superior in control and grafted animals relative to the lesion-only group. These results confirmed that grafts of a human cell line were able to promote recovery to control level in rats that showed marked deficits in spatial learning and memory following substantial (80%-90%) unilateral depletion of forebrain acetylcholine.